UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/616,371	03/15/1996	JONATHAN S. STAMLER	DUK96-03PA	3375

21005 7590 08/10/2004

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
530 VIRGINIA ROAD
P.O. BOX 9133
CONCORD, MA 01742-9133

EXAMINER	
CELSA, BENNETT M	
ART UNIT	**PAPER NUMBER**
1639	

DATE MAILED: 08/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/616,371	STAMLER, JONATHAN S.	
	Examiner	Art Unit	
	Bennett Celsa	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4,16-30,33 and 34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *4 and 22-25* is/are allowed.

6)☒ Claim(s) *16-21, 26-30, 33 and 34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

Applicant's amendment dated 5/17/04 is hereby acknowledged.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of the Claims

Claims 4, 16-30 and 33-34 are currently pending and under consideration.

Allowable Subject Matter

Claims 4 , 22-25 are allowable over the prior art of record which fails to disclose or suggest methods for preserving organ tissue and treating sickle cell anemia using S-nitrosated hemoglobin alone or in combination with a low molecular weight thiol.

Withdrawn Objection (s) and/or Rejection (s)

Applicants arguments have overcome the rejection of claims 4, 16-19, 21-27 and 29-30 under 35 U.S.C. 102(e) as being anticipated, or in the alternative obvious over Stamler et al., US Pat. No. 6,153,186 (11/00: effectively filed 9/95 by 60/003,801).

Applicant's arguments have overcome the rejection of claims 16-21, 26-30 of this application which are in conflict with claims which are present in Application No.08/667,003.

Applicant's arguments have overcome the rejection of claims 4, 16-19, 21-27 and 29-30 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of Stamler et al. US Pat. No. 6,153,186 (11/00: effectively filed 9/95 by 60/003,801).

Outstanding Objection (s) and/or Rejection (s)

Claim Rejections - 35 USC § 102/103

1. Claims 16-21 and 26-30 are rejected under 35 U.S.C. 102(e) as being anticipated by, or alternatively under 35 USC 103 as being obvious over Stamler et al. US Pat. No. 6,583,113 (6/03: filed 3/95 or earlier).

Stamler et al teaches (claims and discloses)compositions comprising nitrosylated heme proteins (including (S) nitrosated/nitrosylate hemoglobin), their intermediate low mw nitrosothiols (e.g. see col. 1) and the use thereof to deliver NO/O2 to tissues for the prevention/treatment of various diseases/disorders including cardiovascular/respiratory diseases/disorders (e.g. ARDS, heart disease etc.) . See e.g. col .1-2 ; col. 4; col. 5; col. 9-12; examples; patent claims. The reference teaching of utilizing NO donating compounds to deliver NO/O2 to tissues (e.g. for therapeutic purposes) would anticipate or alternatively render obvious the use of blood substitutes which would additionally incorporate NO donating hemoglobin compounds to deliver oxygen. Deoxy- hemoglobins are within the scope of the disclosed/patented invention (as immediately envisaged) or alternatively represents an obvious variant thereof of oxy-hemoglobins. The reference teaching of delivering S-nitrosylated Hb to the same host in the same way would inherently result in "scavenging oxygen radicals" E.g. The prior art procedure inherently meets claim limitations because the same protein is applied in the same way in the same amount. *In re Best*, 195 USPQ 430,433 (CCPA 1977); *Ex parte Novitski*, 26 USPQ2d 1389 (B.P.A.I, 1993). Further, the reference discloses the treatment of damaged blood vessels as well as the prevention/treating of

cardivasular/respiratory diseases (e.g. heart disease and ARDS) . See claims and col. 1-4; patent claims. Deoxy- hemoglobins are within the scope of the disclosed/patented invention (as immediately envisaged) or alternatively represents an obvious variant thereof of oxy-hemoglobins. The reference teaching of vasodilation (e.g. see examples) would anticipate or render obvious the use of NO donors, such as S-nitrosated Hb and low mw S-nitrosothiols for treating hypertension.

Discussion

Applicant's arguments directed to the above 102/103 rejection over the 6,583,113 patent were considered but deemed nonpersuasive for the following reasons.

Applicant first notes that the Stamler '113 patent reference has the same content as WO 93/09806 with the exception of the claims and then argues that there is no evidence presented in US Patent No. 6,583,113 that any form of nitrosated or nitrated hemoglobin has any biological activity that can be applied to any disease or medical condition (e.g. no physiological effect).

This argument was considered but deemed nonpersuasive for the following reasons.

The rejection above clearly points out that Stamler et al '113 patent reference teaches that nitric oxide (NO adducts) (e.g upon administration) and S-nitrosothiols (e.g. upon administration or formed in vivo upon NO adduct administration) cause vasodilation and platelet inhibition (e.g. see col 1; examples, particularly Ex. 7) which prevents thrombus formation (e.g. see columns. 2 and 4) for treating/preventing

cardiovascular disorders (e.g. "A disorder resulting from platelet activation or adherence") including cardiac failure,myocardial infarction, heart disease, ARDS etc. (e.g. see col. 4, claims 1-4).

Applicant further alleges that "One of ordinary skill in the art would conclude from Example 19 of 6,583,113 that the syntheses of SNO-hemoglobin failed.

This argument is not found persuasive since applicant has not provided sufficient facts or other evidence to challenge the presumed validity afforded US Pat. No. 6,583,113.

Applicant argues that the teachings of Stamler et al. (US Patent No. 6,583,113:Example 19) is equivalent to WO 93/09806; and that the WO 93 reference fails to teach a method of making S-nitrosylhemoglobin; nor is it enabling in view of the Stamler 132 Declaration mailed February 27, 1998 and Declaration of Joseph Bonaventura dated March 12, 1998 attacking Example 19 of WO 93.

Initially it is noted that the claimed subject matter of US Pat. No. 6,583,113 is presumed valid e.g. enabled.

Further, with respect to S-nitrosylation of proteins including hemoglobin , Stamler WO93 and US Pat. 6,583,113 disclose different methods for thiol nitrosylation of proteins not addressed by the Stamler or Bonaventura Declarations (e.g. as disclosed on page 30-31 of the WO 93 document and col. 15-17 of '113 patent) which include:

1. reaction of nitrosylating agent (e.g. equimolar amounts of acidic NaNo2 as nitrosating agent in a buffered saline at pH 7.4 for tPA);

2. exposure of the protein (e.g. tPA to NO gas in buffered saline)

With regard to the above, Stamler WO 93 further notes that other oxides of nitrogen can be utilized (e.g. NOCL, N2O3) as well as other nitroso equivalents. Optimization of reaction conditions, including pH, is within the skill of the art. Accordingly, the WO 93 and the issued patent reference clearly teaches synthesizing thionitrosylated hemoglobin by using optimized amounts (e.g. nitrosating agent, low molecular weight S-nitrosothiol), with further optimization of pH during nitrosylation to form a more stable nitrosylated oxy/deoxy hemoglobin.

Accordingly, the above rejection is hereby maintained.

2. Claims 18-21 and 26-30 are rejected under 35 U.S.C. 102(e) as being anticipated, or alternatively under 35 USC 103 as being obvious over Stamler et al. US Pat. No. 6,471,978 (10/02: filed 6/2/95 or earlier).

Stamler et al. teach compositions that comprise nitric oxide (NO adducts) (e.g upon administration), including S-nitrosothiols (e.g. upon administration or formed in vivo upon NO adduct administration) cause vasodilation and platelet inhibition (e.g. see col 1) which prevents thrombus formation (e.g. see col. 2). Accordingly, the reference teaches that an administered "nitric oxide adduct" (e.g. a compound or a device comprising a compound: see col. 4) treats damaged vasculature which are susceptible to thrombus formation (e.g see col. 3). The selection of "nitric oxide adducts" of hemoglobin (e.g. (S) nitrosated/nitrated/polynitrosated) is anticipated or in the alternative obvious since hemoglobin is a preferred (e.g. claimed embodiment) "nitric oxide adduct" ie. includes nitrosohemeproteins, with hemoglobin being preferred. Eg.

See patent claims 1, 18-24; 30, 36-42,48, and 54-60); *In re Schaumann*, 572 F.2d 312. 197 USPQ 5 (CCPA 1978). Additionally, the reference teaches combination of S-nitrosothiols with hemoglobin for their expected NO donating properties and thus would potentiate NO (and oxygen) delivery. The reference teaching of compositions comprising nitrosated/nitrosylated hemoglobins and/or low MW S-nitrosothiols for administration would inherently, upon administration, produce the scavenging of oxygen free radicals as reduced blood pressure (E.g. vasodilatory effect).. E.g. The prior art procedure inherently meets claim limitations because the same protein is applied in the same way in the same amount. *In re Best*, 195 USPQ 430,433 (CCPA 1977); *Ex parte Novitski*, 26 USPQ2d 1389 (B.P.A.I, 1993). Further, the reference discloses the treatment of damaged blood vessels as well as the prevention/treating of cardivasular/respiratory diseases (e.g. heart disease and ARDS) . See claims and col. 1-4; patent claims. Deoxy- hemoglobins are within the scope of the disclosed/patented invention (as immediately envisaged) or alternatively represents an obvious variant thereof of oxy-hemoglobins.

Discussion

Applicant's arguments directed to the above 102/103 rejection were considered but deemed nonpersuasive for the following reasons.

Applicant alleges that 6,471,978 (col. 19, lines 6-19) describes methods of producing S-nitroso proteins which are not enabling to one of ordinary skill in the art to produce S-nitroso proteins or any other form of nitrosated/nitrated hemoglobins based on these methods since no

information on the stability and/or biological activity of any hemoglobin derivative is given, or on its suitability as a coating for a medical device.

Applicant's argument was considered but not found persuasive for several reasons.

Initially, it is noted that neither applicant's claims, nor the '978 patent reference teachings are limited to S-nitrosylation but encompass the nitrosylation of additional nucleophilic protein (e.g. hemoglobin) groups. In this regard, the patent discloses (e.g. see col. 19-20 and examples) several different protocols for the (mono/poly) nitrosation/nitration of nucleophilic protein groups (e.g. thiol or otherwise), including hemoglobin. Applicant has neither provided sufficient facts nor other evidence to challenge the reference teaching nor the presumed validity afforded US Pat. No. 6,471,978.

Applicant further argues that the '978 patent fails to teach the combination of S-nitrosothiols with hemoglobin or S-nitrosohemoglobin e.g. to potentiate NO or oxygen delivery.

Applicant's argument was considered but deemed nonpersuasive for the following reasons.

Present claim 30 (being referred to by applicant) is directed to a method for regulating NO/O2 delivery by administering to a mammal a "low molecular weight thiol or nitrosothiol and S-nitrosohemoglobin". As pointed out in the rejection above, the reference (e.g. col .1-2 ; col. 4; col. 5; col. 9-12) teaches nitric oxide releasing, delivering or transferring compounds (e.g. NO adducts) which include nitrosothiols and low mw S-nitrosothiols (E.g. S-nitrosothiol, S-nitrosoamino acids etc.) as well as higher mw S-nitrosothiols, including S-nitrosylated proteins containing heme including hemoglobin with its oxygen carrying/transferring capacity. Thus, the combination of a low mw (S) nitrosothiol with a

high molecular weight (S) nitrosolyated heme protein particularly (S)nitrosylated hemoglobin is suggested by the reference teaching.

Accordingly, the above rejection is hereby maintained.

Claim Rejections - 35 USC § 103

3. Claims 33-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stamler et al, WO 93/09806 (5/93) or its U.S. equivalent US Pat. 6,291,424 (9/01: filed 3/95 or earlier).

US Pat. No. 6,291,424 (claiming S-nitrosated hemoglobins) and WO 93/09806 appear to contain identical disclosures and are equally applicable in the present rejection. However, for the purposes of brevity, the present rejection will be discuss the WO 93 document.

The presently claimed invention is directed to producing a composition comprising either SNO-Hb[FeII]O2 (produced in the presence of oxygen) or SNO-Hb[FeII] (produced in the absence of oxygen) by reacting "excess nitrosating agent" (e.g. low molecular weight nitrosothiols i.e. S-nitroglutathione et.al.) with purified hemoglobin (e.g. claims 10-11 and 13-14). Claims 12 and 15 specifically select a low molecular weight S-nitrosothiol as the nitrosating agent.

Stamler discloses different methods for thiol nitrosylation of proteins (as disclosed on page 30-31) which include:

1. reaction of nitrosylating agent (e.g. equimolar amounts of acidic NaNo2 as nitrosating agent in a buffered saline at pH 7.4 for tPA);

2. exposure of the protein (e.g. tPA to NO gas in buffered saline)

With regard to the above, Stamler further notes that other oxides of nitrogen can be utilized (e.g. NOCL, N2O3) as well as other nitroso equivalents.

However, the above two reference methods for thiol nitrosylation fail to disclose the use of "excess" nitrosating agent, and preferably the selection of a low molecular weight S-nitrosothiol as the nitrosating agent for thionitrosylation of hemoglobin.

But the Stamler reference (e.g. Example 19 on pages 58-59) specifically discloses the preferential selection of a low molecular weight S-nitrosothiol (e.g. SNOAC) instead of acidic Na NO2 as utilized for tPA due to reduced ability of the SNOAC as compared with acidic nitrate to bind at the redox metal which reduces oxygen binding affinity.

Further, the use of "excess nitrosating agent" in either reaction 1. or 2 above is suggested by the Stamler reference since providing a greater concentration of NO serves to enhance the therapeutic efficacy of the nitrosylated proteins (e.g. see bottom of page 23-top of 24)

It is further noted that the use of higher pH values (e.g. pH 7.4) than that utilized in the thionitrosylated hemoglobin example (e.g. pH 6.9 Example 19) is also suggested by the reference since thionitrosylated proteins are known to be stable under physiological conditions (e.g. TBS, pH 7.4, room temperature: see page 31) and further the reference discloses the use of pH7.4 in the the making and storage of vaious thiol proteins. Additionally, the thiol-protein synthetic steps are analogous to that of Example 19: see page 30, lines 20-27; page 33, lines 20-26).

Optimization of reaction conditions, including pH, is within the skill of the art.

Additionally, it is a matter of obvious design choice to select anaerobic conditions for making a deoxygenated hemoglobin derivative and aerobic conditions when desiring to make an oxygenated hemoglobin derivative.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of applicant's invention to synthesize thionitrosylated hemoglobin by using "excess" nitrosating agent, and preferably a low molecular weight S-nitrosothiol, and to further optimize pH during nitrosylation to utilize physiological conditions to form a more stable nitrosylated oxy/deoxy hemoglobin.

Discussion

Applicant's arguments directed to the above obviousness rejection were considered but deemed nonpersuasive for the following reasons.

Applicant alleges that one of ordinary skill in the art would conclude from Example 19 of 6,291,424 that the syntheses of SNO-hemoglobin failed.

This argument is not found persuasive since applicant has not provided sufficient facts or other evidence to challenge the presumed validity afforded US Pat. No. 6,291,424.

Applicant argues that the teachings of Stamler et al. (US Patent No. 6,291,424:Example 19) is equivalent to WO 93/09806; and that the WO 93 reference fails to teach a method of making S-nitrosylhemoglobin; nor is it enabling in view of the Stamler 132 Declaration mailed February 27, 1998 and Declaration of Joseph Bonaventura dated March 12, 1998 attacking Example 19 of WO 93.

Initially it is noted that the claimed subject matter of US Pat. No. 6,291,424 is presumed valid e.g. enabled.

Further, with respect to S-nitrosylation of proteins including hemoglobin , Stamler WO93 and US Pat. 6,291,424 disclose different methods for thiol nitrosylation of proteins not addressed by the Stamler or Bonaventura Declarations (e.g. as disclosed on page 30-31 of the WO 93 document and col. 15-17 of '113 patent) which include:
1. reaction of nitrosylating agent (e.g. equimolar amounts of acidic NaNo2 as nitrosating agent in a buffered saline at pH 7.4 for tPA);
2. exposure of the protein (e.g. tPA to NO gas in buffered saline)
With regard to the above, Stamler WO 93 further notes that other oxides of nitrogen can be utilized (e.g. NOCL, N2O3) as well as other nitroso equivalents. Optimization of reaction conditions, including pH, is within the skill of the art. Accordingly, the WO 93 and the issued patent reference clearly teaches synthesizing thionitrosylated hemoglobin by using optimized amounts (e.g. nitrosating agent, low molecular weight S-nitrosothiol), with further optimization of pH during nitrosylation to form a more stable nitrosylated oxy/deoxy hemoglobin.

Applicant argues that neither the WO 93/09806 nor its US Patent equivalent disclose the use of pH 7.4 in any attempts to produce any S-nitrosoproteins.

This argument was considered but deemed nonpersuasive for the following reasons.

As pointed out in the above rejection, the use of higher pH values (e.g. pH 7.4) than that utilized in the thionitrosylated hemoglobin example (e.g. *pH 6.9* Example 19) is

suggested by the reference since thionitrosylated proteins are known to be stable under physiological conditions (e.g. TBS, pH 7.4, room temperature: see page 31) and further the reference discloses the use of pH7.4 in the the making and storage of vaious thiol proteins. Additionally, the thiol-protein synthetic steps are analogous to that of Example 19: see page 30, lines 20-27; page 33, lines 20-26) and the reaction of the nitrosylating agent (e.g. equimolar amounts of acidic NaNo2) regarding the thionitrosylation of proteins other than hemolglobin (e.g. tPA) occurs in a buffered saline at pH 7.4. Still further, as pointed out in the rejection above, optimization of reaction conditions, including pH, is within the skill of the art.

Accordingly, the above rejection is hereby maintained.

Double Patenting

Claims 19-21, 26-30 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-17 (especiallyclaims 7-9 and 17) of copending Application No. 10/216,865 (PG PUB US 2003/0079674A1 Jan 9, 2003).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the application claims compositions comprising S- nitroso hemoglobins and uses thereof which comprise NO delivery, including treating/preventing cardiovascular/respiratory disorders (e.g. Heart disease, ARDS etc: see patent claim 9 interpreted in light of disclosure: e.g. at page 6). Deoxy- hemoglobins are within the scope of the disclosed/patented invention (as immediately envisaged) or alternatively represents an obvious variant thereof of oxy-hemoglobins. The adminsitration of hemoglobins to patients for the

treatment of cv/pulmonary disorders would inherently result in the scavenging of oxygen free radicals and/or the reduction of blood pressure (e.g. vasodilatory effect).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Discussion

Applicant's arguments directed to the above provisional double patenting rejection were considered but deemed nonpersuasive for the following reasons. Initially, it is noted that the above rejection was revised to remove claims 16-18 drawn to a blood substitute.

Applicant argues that the claims of copending Application No. 10/216,865 do not render obvious the presently claimed invention and requests clarification in this regard. Additionally, applicant argues that S-nitrosohemoglobin is not taught by the patent claims.

This argument was considered but deemend nonpersuasive for the following reasons. The above rejection clearly points out how the claims render obvious the presently claimed invention. In this regard the patent claims clearly teach delivering (e.g. administering) nitric oxide or regulating oxygen delivery to body sites by utilizing S-nitrosohemoglobin (e.g. patent claims 5-7, 17) and for treating disease states by adminstering the same compound, including disease states (e.g. cardiovascular and respiratory disorders) within the scope of the presently claimed invention (e.g. see patent claim 9). Accordingly, the claims compositions comprising S- nitroso hemoglobins and uses thereof which comprise NO delivery, including treating/preventing cardiovascular/respiratory disorders (e.g. Heart disease, ARDS etc: see patent claim 9

interpreted in light of disclosure: e.g. at page 6) . The adminsitration of hemoglobins to patients for the treatment of cv/pulmonary disorders would inherently result in the scavenging of oxygen free radicals and/or the reduction of blood pressure (e.g. vasodilatory effect). In this regard, it is noted that courts have acknowledged that patent claims are not interpreted in a vacuum, and reference back to the patent's specification for *purposes of claim interpretation* (e.g. determine what is being claimed), even in the context of double patenting, is acceptable. E.g. *In re Higgins et al.* (CCPA 1966) 369 F2d 414, 152 USPQ 103. Additionally, in satisfying the Examiner's burden of demonstrating *inherency of a claim limitation* any source of "extrinsic evidence" is permissible [(e.g. citation of references or other evidence: See MPEP 2131.01(d); See *In re Best*, 195 USPQ 430,433 (CCPA 1977)(inherent anticipation regarding prevention);], as well as the use of "intrinsic" evidence, which include applicant's own specification . *See Ex parte Novitski*, 26 USPQ2d 1389 (B.P.A.I, 1993) (Board consulted applicant's own Experimental Results to demonstrate inherency of method preamble limitation).

Applicant further argues that Jonathan Stamler is not an inventor of the subject matter of 10/216,865 as evidenced by his failure to sign the declaration in that application and thus there is no common inventor with the present application, thus precluding double patenting.

This argument is not persuasive since the 10/216,865 application still lists Dr. Stamler as an inventor.

Accordingly, the above rejection is hereby maintained.

Claims 19-21, 26-30 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 6,583,113 (6/03). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims teach compositions comprising nitrosated/nitrosylated heme proteins (e.g.including S-nitrosylated hemoglobins : see cliams 1-3) and their use (E.g. delivery of NO to tissues via administration) in treaing/preventing diseases including cardiovascular diseases such as ARDS (E.g. see claims 1 and 4:col. 11-12) and heart disease. Deoxy- hemoglobins are within the scope of the disclosed/patented invention (as immediately envisaged) or alternatively represents an obvious variant thereof of oxy-hemoglobins.

Discussion

Applicant's arguments were considered but deemed partially persuasive for the following reasons. Initially, it is noted that the above rejection has been revised to remove claims 16-18.

Applicant argues that claims 1-4 of US 6,583,113 does not comprise a step of administering to a human a composition comprising a nitrosated/nitrosylated hemoglobin and additionally claims 1-4 read on a process that occurs naturally in nature (e.g. red blood cells).

Applicant's arguments were considered but deemed nonpersuasive for the following reasons.

Initially, whether the patent claims encompass "a process that occurs in nature" is not germaine as long as the patent claims encompass the presently claimed process

steps. As pointed out in the above rejection, Patent claim 1 teaches preventing or treating " a disease or disorder in a "patient" in need thereof" comprising "delivering"nitric oxide to a targeted site in the body of a patient using a nitrosated and/or nitrosylated "heme protein", wherein the heme protein is nitrosated and/or nitrosylated at one or more thiol groups in the heme protein. "Delivery" to a "patient in need thereof" clearly encompasses administration of a pharmaceutical composition to a human or animal as presently claimed. (See e.g. patent columns 4-5). Patent claims 2-4 specify that the "heme protein" is hemoglobin (e.g .human) and that the "disease or disorder" encompasses " (cardiovascular) disorder(s) resulting from platelet activation or adherence" such as myocardial infraction . The term "delivery" to a "patient in need thereof" clearly encompasses administration of a pharmaceutical composition to a human or animal as presently claimed. For example, the '113 patent specification (e.g. col. 4) establishes that the claimed "delivery" of nitrosylated/nitrosated hemoglobin to a "patient" to "effect vasodilation, platelet inhibition and thrombolysis" (inherently) as well as treat "cardiovascular disorders" clearly encompass "administration" of pharmaceutical compositions to patients which are "human" and/or "animal" within the scope of the presently claimed invention. See e.g. '113 col. 4-5 and examples.

Applicant further argues that the office erroneously failed to arrive at the correct inventorship result regarding a Rule 1.63 petition in the 09/092,622 application (now US 6,291,424) which is the parent of 09/835,038 (now US 6,583,113) which would have removed Dr. Stamler as an inventor of US 6,583,113; thus rendering double patenting inapplicable.

This argument is not persuasive since the issued patent, presumed valid, lists Dr. Stamler as an inventor. Accordingly, the above rejection is hereby maintained.

Claims 19-21, 26-30 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-65 of Stamler et al. US Pat. No. 6,471,978 (10/02: filed 6/2/95 or earlier) as interpreted in light of the specification regarding the scope of treatment of vasculature damage and inherency.

Stamler et al. teach (e.g. disclose and claim) compositions that comprise nitric oxide (NO adducts) (e.g upon administration), including S-nitrosothiols (e.g. upon administration or formed in vivo upon NO adduct administration) cause vasodilation and platelet inhibition (e.g. see col 1) which prevents thrombus formation (e.g. see col. 2). Accordingly, the reference teaches that an administered "nitric oxide adduct" (e.g. a compound or a device comprising a compound: see col. 4) treats damaged vasculature which are susceptible to thrombus formation (e.g see col. 3). The selection of "nitric oxide adducts" of hemoglobin (e.g. (S) nitrosated/nitrated/polynitrosated) is anticipated or in the alternative obvious since hemoglobin is a preferred (e.g. claimed embodiment) "nitric oxide adduct" ie. includes nitrosohemeproteins, with hemoglobin being preferred. Eg. See patent claims 1, 18-24; 30, 36-42,48, and 54-60); *In re Schaumann*, 572 F.2d 312. 197 USPQ 5 (CCPA 1978). Additionally, the reference teaches combination of S-nitrosothiols with hemoglobin for their expected NO donating properties thus anticipating or rendering obvious present claims directed to "potentiation of NO delivery". The reference teaching of compositions comprising nitrosated/nitrosylated hemoglobins

and/or low MW S-nitrosothiols for administration would inherently, upon administration, produce the scavenging of oxygen free radicals as reduced blood pressure (E.g. vasodilatory effect).. E.g. The prior art procedure inherently meets claim limitations because the same protein is applied in the same way in the same amount. *In re Best*, 195 USPQ 430,433 (CCPA 1977); *Ex parte Novitski*, 26 USPQ2d 1389 (B.P.A.I, 1993). Further, the reference discloses the treatment of damaged blood vessels as well as the prevention/treating of cardivasular/respiratory diseases (e.g. heart disease and ARDS) See claims and col. 1-4; patent claims. Deoxy- hemoglobins are within the scope of the disclosed/patented invention (as immediately envisaged) or alternatively represents an obvious variant thereof of oxy-hemoglobins.

DISCUSSION

Applicant's arguments were considered but deemed nonpersuasive for the following reasons. Initially, it is noted that the above rejection has been revised to remove claims 16-18.

Applicant requests clarification as to how the patent disclosure is being used and where inherency is being applied relative to the patent claims.

The argument was considered but deemed nonpersuasive for the following reasons. The above rejection provides ample guidance regarding how the present claims are rendered obvious and how inherency is applied in the context of rendering obvious claim limitations. For example, Stamler et al. teach (e.g. see patent claims 1, 30, 48,) that nitric oxide (NO adducts) and S-nitrosothiols, upon in vivo administration (e.g. local or systemic: see patent claims 5 and 6; i.e. to a "patient" who is a "human" or "animal" w/n the scope of the present claims: see '978 abstract) prevents/inhibits platelet deposition and "alleviates"

(e.g. treats) restenosis and cardiovascular/respiratory diseases (e.g. see col 1; patent claims 1-4) which represents a disease or medical condition characterized by NO/O2 metabolism abnormalities as broadly claimed. Accordingly, the patented invention teaches the administration (e.g. local/systemic) of "nitric oxide adducts" to: a. inhibit platelet activation and b. prevent/inhibit/treat "a disorder resulting from platelet activation or adherence in an animal or human" (e.g. restenosis or damaged vasculature) c. treat cv/respiratory disorders within the scope of present claims Further, the selection of "nitric oxide adducts" of modified hemoglobin (e.g. (S) nitrosated) is anticipated or in the alternative obvious since hemoglobin is a preferred (e.g. claimed embodiment). Eg. See patent claims 1, 18-24; 30, 36-42,48, and 54-60). See *In re Schaumann*, 572 F.2d 312. 197 USPQ 5 (CCPA 1978

Applicant argues that patent claims 1-65 require "a damaged vascular surface" not required by the present claims.

This argument was considered but deemed nonpersuasive.

The above rejection details how the patent claims provide a teaching of dministering(e.g. local/systemic etc.) nitrous oxide releasing compounds (e.g. nitrous oxide adducts) including SNO-Hb for use in methods within the scope of the presently claimed invention.

Applicant argues that the "class of agents" in claims 1-65 of 6,471,978 is extremely broad and includes compounds with no demonstrated ability to release NO and therefore it is not true that "the same protein is applied in the same way in the same amount".

This argument was considered but deemed nonpersuasive.

The above rejection clearly points out that several different sets of dependent patent claims carve out a "preferred" embodiment of nitrous oxide adducts (e.g. NO donating) compounds which encompass modified hemoglobin e.g. (S) nitrosated the selection of which is anticipated or rendered obvious by these dependent patent claims. Eg. See patent claims 1, 18-24; 30, 36-42,48, and 54-60).

Applicant argues that "[I]t is not apparent to one of ordinary skill in the art why agents that must be applied to a damaged vascular surface for the purpose of treating that damage vascular surface, and are not effective if administered systemically (see Figure 3 and column 28, line 58 to column 29, line 3) would have any effect on platelet aggregation in an animal or human."

This argument was considered but deemed nonpersuasive for the following reasons.

As discussed above, the patent claims provide a teaching of administering (e.g. *local/systemic* etc.) NO releasing compounds (e.g. nitrous oxide adducts) to treat diseases/medical conditions resulting from abnormal NO/O2 within the scope of the presently claimed invention. Figure 3 and column 28, line 58 to column 29, line 3 referred to by applicant merely disclose that iodine labelled S-NO-BSA administered locally and systemically to balloon-injured rabbit femoral artery binds more when administered locally as compared to systemically. It is noted, however, that systemic administration still shows greater binding as compared to a control. In this regard it is noted that the patent claims (and Figure 3) teach both local and systemic administration (e.g patent claims 5 and 6) which is within the scope of the presently claimed invention.

Additionally, the example addresses S-NO-BSA and not the corresponding hemoglobin derivative; and in any event does achieve some degree of systemic binding

Applicant queries why the Examiner refers to the patent specification when the patent claims, for purposes of double patenting are at issue; and questions the applicability of *In re Schaumann* decision in the present context (e.g. double patenting rejection).

These arguments were considered but deemed nonpersuasive for the following reasons.

Initially, it is noted that courts have acknowledged that patent claims are not interpreted in a vacuum, and reference back to the patent's specification for *purposes of claim interpretation* (e.g. determine what is being claimed), even in the context of double patenting, is acceptable. E.g. *In re Higgins et al.* (CCPA 1966) 369 F2d 414, 152 USPQ 103. Additionally, in satisfying the Examiner's burden of demonstrating *inherency of a claim limitation* any source of "extrinsic evidence" is permissible [(e.g. citation of references or other evidence: See MPEP 2131.01(d); See *In re Best*, 195 USPQ 430,433 (CCPA 1977)(inherent anticipation regarding prevention);], as well as the use of "intrinsic" evidence, which include applicant's own specification . *See Ex parte Novitski*, 26 USPQ2d 1389 (B.P.A.I, 1993) (Board consulted applicant's own Experimental Results to demonstrate inherency of method preamble limitation). Accordingly, for purposes or demonstrating claim limitation inherency or claim interpretation, the use of "intrinsic evidence" (e.g. within the four corners of the specification) is entirely proper; even in the context of double patenting.

Applicant's argument fails to appreciate the patent claims (e.g. especially the dependent claims) teaching as a whole which anticipates or render obvious the selection of modified hemoglobins in a manner consistent with *In re Schaumann*, 572 F.2d 312. 197 USPQ 5 (CCPA

1978). With respect to anticipation and obviousness regarding a reference teaching of a limited genus or markush listing of compounds applicant is further referred to MPEP 2131.02 (anticipation) and MPEP 2144.08 (obviousness) both of which sections further discuss the *In re Schaumann* CCPA decision. Thus, the rejection above properly makes reference to the '978 specification for purposes of claim interpretation and inherency.

Accordingly, for all the reasons recited above, the double patenting rejection is hereby retained.

Claims 16-21, 26-30 of this application conflict with claims which are present in Application No. 08/796,164.

37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

Discussion

Applicant's arguments directed to the above were considered but deemed non persuasive for the following reasons.

Applicant argues that the 08/796,164 application claims were found to differ in scope and meaning from the claims of the subject application.

The Examiner appreciates applicant's attempt to maintain a clear line of demarcation. However, since prosecution is continuing in both cases, the above rejection will be maintained until allowable subject matter is determined in either application in order for the Examiner to make a judgement regarding the necessity of claim cancellation (e.g 101 double patenting rejection) or the need for a terminal disclaimer (e.g. double patenting rejection). To the extent the present claims are narrower and would represent a species within the 08/796,164 application claims, this rejection can be obviated by the filing of a terminal disclaimer.

In this regard, the Examiner also respectfully requests applicant's continued assistance in locating related (e.g. Stamler as applicant) applications which are claiming similar subject matter.

Accordingly, the above rejection is hereby maintained.

Conclusion

THIS ACTION IS MADE FINAL.

Applicant is reminded of the extension of time policy as set forth in 37CFR 1.136(a).A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however,

will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Future Correspondences

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bennett Celsa whose telephone number is 571-272-0807. The examiner can normally be reached on 8-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-273-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Bennett Celsa
Primary Examiner
Art Unit 1639

BC
August 6, 2004